Insulin

Insulin (see Annotation J-3 Insulin Therapy)

- Efficacy: Dose can be adjusted to achieve a wide range of glucose lowering
- Requires intensive patient education
- Regular, neutral protamine Hagedorn insulin [NPH], and lente – inexpensive
- Insulin analogs – moderately expensive

Contraindications: Hypersensitivity to insulin

Adverse Events: Hypoglycemia, hypersensitivity, injection site reactions, weight gain

Insulin	Onset (hours)	Peak (hours)	Duration (hours)	Compatible Mixed With	Appearance
RAPID-ACTING					
Regular (Novolin R®, Humulin R®)	0.5 – 1	2 – 5	6 – 10	NPH, lente, ultralente	Clear
Lispro (Humalog®)	0.25 – 0.5	0.5 – 2.5	3 – 6.5	Human NPH, human ultralente[c,d]	Clear
Aspart (Novolog®)	0.17 – 0.33	1 – 3	3 – 5	Human NPH [c,e]	Clear
INTERMEDIATE-ACTING					
NPH (Novolin N®, Humulin N®)	1 – 1.5	4 – 12	16 – 24	Regular	Cloudy
Lente (Novolin L®, Humulin L®)	1 – 2.5	7 – 15	16 – 24	Regular	Cloudy
LONG-ACTING					
Ultralente (Humulin U®)	4 – 6	8 – 20	24 – 28	Regular	Cloudy
Insulin glargine (Lantus®)	1.1	2 – 20	Up to 24	Not to be mixed with other insulins	Clear

Insulin (cont.)

Insulin (see Annotation J-3 Insulin Therapy) cont.

Insulin	Compatible Mixed With	Appearance
PRE-MIXED PRODUCTS		
70% NPH/ 30% Regular (Novolin 70/30, Humulin 70/30); 50% NPH/ 50% regular (Humulin 50/50)	Not to be mixed with other insulins	Cloudy
75% intermediate/25% lispro (Humalog mix 75/25)	Not to be mixed with other insulins	Cloudy

[a] Adapted from AHFS Drug Information, American Society of Health-System Pharmacists, Inc., 2002
[b] The time course of action is intended as a general guide as many factors may influence these parameters (e.g., type of preparation, dose, site of administration, and patient-related variables).
[c] The effects of mixing insulin lispro or insulin aspart with insulins of animal source have not been studied.
[d] The only animal source insulin remaining on the market is purified pork as regular, NPH, and lente.
[e] The effects of mixing insulin lispro with insulins produced by manufacturers other than Eli Lilly has not been studied.
[e] The effects of mixing insulin aspart with insulins produced by manufacturers other than Novo Nordisk has not been studied.

Determination of Target HbA_1c Level

Major Comorbidity(d) or Physiologic Age	Microvascular Complications		
	Absent or Mild (a)	Moderate (b)	Advanced (c)
Absent >15 years life expectancy	**7%** (<1% above upper normal range)	**<8%** (<2% above upper normal range)	**<9%** (<3% above upper normal range)
Present (e) 5 – 15 years life expectancy	**<8 %** (<2% above upper normal range)	**<8%** (<2% above upper normal range)	**<9%** (<3% above upper normal range)
Marked (f) <5 years life expectancy	**<9%** (<3% above upper normal range)	**<9%** (<3% above upper normal range)	**<9%** (<3% above upper normal range)

(a) Mild microvascular disease is defined by early background retinopathy, and/or microalbuminuria, and/or mild neuropathy.
(b) Moderate microvascular disease is defined by pre-proliferative (without severe hemorrhage, intra-retinal microvascular anomalies [IRMA], or venous bleeding) retinopathy or persistent, fixed proteinuria (macroalbuminuria) and/or demonstrable peripheral neuropathy (sensory loss).
(c) Advanced microvascular disease is defined by severe non-proliferative (with severe hemorrhage, IRMA, or venous bleeding) or proliferative retinopathy and/or renal insufficiency (serum creatinine level > 2.0 mg/dL) and/or insensate extremities or autonomic neuropathy (e.g., gastroparesis, impaired sweating, or orthostatic hypotension).
(d) Major comorbidity includes, but is not limited to, any or several of the following conditions: cardiovascular disease, chronic obstructive pulmonary disease, chronic liver disease, stroke, and malignancy.
(e) Moderate degree of major comorbid condition.
(f) Severe degree or end-stage major comorbid condition.

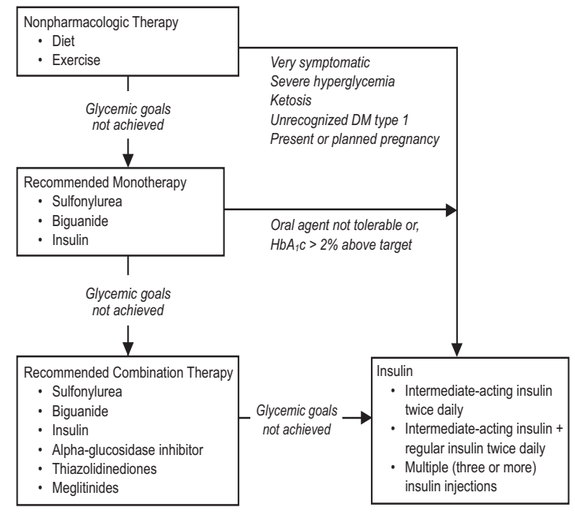
Sequential Treatment for Type 2 DM

	Therapy	Drugs	Expected HbA_1c reduction Over a 2 – 3 month period of follow-up
1	Lifestyle modification, diet, and exercise	None	—
2	Lifestyle modification, diet and exercise *and* **Monotherapy** with oral agent or insulin	Sulfonylurea or biguanide	1 – 2%
3	Lifestyle modification, diet and exercise *and* **Combination** (add a second oral agent)	Sulfonylurea + biguanide Sulfonylurea/biguanide + alpha-glucosidase inhibitor Sulfonylurea/biguanide + thiazolidinedione Biguanide + repaglinide/ nateglinide	1 – 2% 0.5 – 1% 0.7 – 1.75% 0.1 – 3%
4	**Insulin** with oral agent	Biguanide + insulin Thiazolidinedione + insulin Sulfonylurea + insulin	0.2 – 2.6%
5	Insulin	Insulin alone	2%
6	Referral	None	—

Carefully selected individuals may benefit from three-drug oral hypoglycemic therapy. In general, such patients may benefit from referral to a diabetes care team.

VA/DoD Clinical Practice Guideline Management of Diabetes Mellitus in Primary Care Pocket Guide

Management of Glycemic Control Update 2003



VA access to full guideline: http://www.oqp.med.va.gov/cpg/cpg.htm
DoD access to full guideline: http://www.qmo.amedd.army.mil
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Oral Pharmacologic Agents

Sulfonylureas

- Efficacy: estimate reduction in HbA_1c = 1.0 – 2.0 %
- 1st generation sulfonylureas are no longer commonly used
- No difference in long-term efficacy or failure rate has been demonstrated among the sulfonylureas
- The preferred agents have shorter half-lives and inactive metabolites
- 1st generation sulfonylureas are 100% renally eliminated. Chlorpropamide and tolazamide have active metabolites.
- Glipizide, glyburide, and glimepiride are renally eliminated by 80 – 85%, 50%, and 60%, respectively. All but glipizide have active metabolites.
- Inexpensive

Agents	Dose		Contraindications	Adverse Events
1st generation				
Chlorpropamide	100 – 500 mg qd		• Hypersensitivity • Pregnancy	• Hypoglycemia • Hypersensitivity • Weight gain
Tolazamide	1000 mg qd or in 2 divided doses			
Tolbutamide	250 – 2000 mg in 2 – 3 divided doses			
2nd generation				
Glimepiride	1 – 4 mg once daily			
Glipizide* Glipizide XL*	2.5 – 40 mg qd or in 2 divided doses 5 – 10 mg once daily	• Taken 30 minutes before a meal • Doses >15 mg should be divided into 2 doses		
Glyburide*	1.25 – 20 mg once daily or in 2 divided doses			
Micronized glyburide*	0.75 – 12 mg once daily or in 2 divided doses	• Doses >6 mg may provide a better response when divided • If the response to a single daily dose of glybride or glipizide does not achieve treatment goals, dividing the dose may be effective		

Biguanide

- Efficacy: estimate reduction in HbA_1c = 1.0 – 2.0%
- The major blood glucose lowering effect is through decreasing hepatic glucose production with some decrease in peripheral insulin resistance
- May restore ovulation in premenopausal anovulatory females
- Monitor renal function prior to drug initiation and at least annually thereafter
- Inexpensive when using generic

Agents	Dose		Contraindications	Adverse Events
Metformin	Initial – 500 mg bid or 850 mg q am Maintenance – 850 mg bid with meals Maximum – 2550 mg/day in 3 divided doses	If on 500 mg bid, dosage increase may be made by 500 mg increments weekly up to 1000 mg bid If on 850 mg q am, dosage increase of 850 mg may be made every other week (given as 850 mg bid) The dose response curve usually plateaus after 2000 mg/day Take with food to avoid possible GI symptoms	**Contraindications** • Renal dysfunction (SCr >1.5 mg/dl for males or >1.4 mg/dl for females) • CHF requiring pharmacologic management • Acute or chronic metabolic acidosis • Hold prior to IV dye procedures and for 48 hours after the procedure. Reinstitute only after renal function is found to be normal. **Not Recommended** • Age ≥80 unless normal creatinine clearance, and the dose should not be escalated to the maximum in elderly patients due to increased susceptibility to lactic acidosis • Hepatic disease or excessive ethanol intake • Withhold in the presence of any condition associated with hypoxemia, dehydration or sepsis	• Potential for lactic acidosis when used in patients for whom the drug is contraindicated • Transient dose-related GI symptoms (diarrhea, nausea, vomiting, bloating, flatulence, anorexia) • Decrease in vitamin B12 levels
Metformin extended release	Initial – 500 mg qd with the evening meal	Dose may be increased by 500 mg per week to a maximum of 2000 mg once daily. If glycemic control is not achieved, consider dividing into 2 doses.		

Alpha-glucosidase inhibitors

- Efficacy: estimate reduction in HbA_1c = 0.4 – 1.0%
- Delays the digestion of carbohydrates, thereby decreasing postprandial hyperglycemia
- Allows for flexible meal dosing
- Moderately expensive

Agents	Dose		Contraindications	Adverse Events
Acarbose Miglitol	Initiate – 25 mg tid Maintenance – 50 mg tid. Maximum – 100 mg tid	Or initiate gradually: 25 mg qd x 1-2 weeks followed by 25 mg bid for 1 – 2 weeks followed by 25 mg tid. Once a 25 mg tid dosing regimen is reached, further increases may be made at a 4 – 8 week intervals. Max dose for acarbose if weight <60 kg = 50 mg tid Dose is to be taken with the first bite of each main meal If the patient misses or adds a meal, he/she should omit or add the dose	**Contraindications** • Presence of intestinal complications (inflammatory bowel disease, colonic ulceration, intestinal obstructions, digestion or absorption disorders) • Acarbose is contraindicated in patients with cirrhosis. Miglitol pharmacokinetics are not altered in cirrhosis and may be used. **Not Recommended** • SCr > 2.0 mg/dl	• Transient dose-related GI symptoms (diarrhea, abdominal pain, flatulence) can limit compliance with therapy • Acarbose, especially at doses greater than 50 mg tid, may cause serum AST/ALT elevation; monitor serum levels every 3 months during the first year of treatment

Thiazolidinediones

- Efficacy: estimate reduction in HbA_1c = 1.0 – 1.5%
- Enhances insulin sensitivity in skeletal muscle, hepatic, and adipose tissue without directly stimulating insulin secretion from the pancreas. Also has a small effect on inhibiting hepatic glucose
- Liver function and bilirubin should be tested every 2 months for 1 year, then periodically thereafter. If ALT is >3x upper limit of normal, recheck another level as soon as possible. If ALT remains >3x the upper limit, discontinue use
- May restore ovulation in premenopausal anovulatory females
- Very expensive

Agents	Dose		Contraindications	Adverse Events
Rosiglitazone Pioglitazone	4 – 8 mg qd or divided into 2 doses 15 – 45 mg qd	May be given without regard to meals, no dosage adjustment required for renal insufficiency, and the current sulfonylurea, metformin, or insulin dose should be continued when adding rosiglitazone or pioglitazone. When using with insulin, if plasma glucose levels decrease to less than 100-120 mg/dL, the dose of insulin should be decreased by 10-25%. Continue to monitor the patient for further adjustments Slow onset of action	**Not Recommended** • New York Heart Association Classes III and IV • Do not initiate in patients with ALT >2.5x the upper limit of normal	• Edema • Weight gain • Decrease Hgb/HCT • Hepatotoxicity (rare)

Meglitinides

- Efficacy: estimate reduction in HbA_1c = 0.6 – 1.9%
- Like sulfonylureas (SFU), it stimulates pancreatic secretion of insulin. It has a faster onset and shorter duration of action than SFUs, therefore postprandial glucose is affected to a greater extent than fasting blood glucose
- Allows for flexible meal dosing
- Do not use in patients who have failed sulfonylurea therapy
- Expensive

Agents	Dose		Contraindications	Adverse Events
Repaglinide Nateglinide	Initial – 0.5 mg in patients with HbA_1c <8%. 1 or 2 mg in patients previously treated with hypoglycemics or if HbA_1c >8% Maximum – 4 mg per meal 120 mg before each meal.	Take 1 – 30 minutes before a meal. If the patient misses or adds a meal, he/she should omit or add the dose	**Use With Caution** **Repaglinide** • Hepatic impairment • Severe renal impairment **Nateglinide** • Moderate-severe hepatic impairment	• Hypoglycemia • Weight gain

*In general, the hypoglycemic effects of glyburide and glipizide tend to plateau at 10 mg and 20 mg, respectively.